ESTROGEN REPLACEMENT THERAPY

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As a consequence of increasing longevity in the human female, clinical problems associated with aging have become more prevalent. Some of the most common and perplexing changes associated with aging are those that evolve from the endocrinologic changes of menopause. Although the terms *menopause* and *climacteric* have generally been used interchangeably, menopause refers to a woman's last physiologic bleeding episode and is only part of the climacteric. The climacteric is the period of transition from the reproductive to the nonreproductive stage of life and, thus, usually begins several years before and extends for a number of years from the most obvious event, menopause (52). This distinction is clinically relevant since some of the changes seen in climacteric females are related to failing ovarian function and may occur in women still menstruating.

The ovaries are the only endocrine glands in women that cease physiologic function long before the end of life. The average age at menopause in this country is 51–52 years (29). Currently, there are approximately 40 million American women over age 50 (60), and these women have an average life expectancy of 28 years after menopause (28). Thus, women can expect to spend approximately one third of their life with reduced ovarian function. These numbers are even larger when one also considers the younger women who have been surgically castrated or in whom premature ovarian failure has occurred. In spite of this there are relatively few substantive investigative studies which address the physiologic and clinical aspects of the perimenopausal and postmenopausal period.

The term *menopausal syndrome* is often used to refer to a variety of symptoms that may occur at this stage in a woman's life. Some of these symptoms may easily be attributed to a relative lack of estrogen secretion, e.g., vasomotor symptoms (hot flushes and perspiration), atrophic changes in the genitourinary system, and other related conditions such as osteoporosis. Other commonly associated symptoms have been less clearly attributed to estrogen deficiency and include headaches, insomnia, irritability, fatigue, mood changes, and nervousness. These are thought more likely to represent psychosociocultural

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disturbances (75). Because the climacteric and other events associated with advancing age are so intertwined, it is difficult to determine clearly the etiology of some of these symptoms.

Although it has been estimated that 85% of postmenopausal women in the United States have some symptoms of estrogen deficiency and that 50–60% percent might benefit from the administration of exogenous replacement of estrogen (35), only 10–25% will present themselves for medical evaluation in regards to the climacteric (75).

Management of the menopausal patient has long created controversy. Since estrogen replacement therapy has been available there have been differing opinions on whether or not patients should receive the medication. Among the group of physicians who feel that estrogen replacement therapy is justified, one can find variations in the indications for therapy, the dosages of the various medications, and the duration of therapy. Because of potential risks, specifically the increased risk of the development of endometrial neoplasia, reassessment of the indications for and safety of estrogen replacement therapy are in order.

This chapter will briefly review the endocrinologic changes of the climacteric and the advantages (benefits) and disadvantages (risks) of estrogen therapy in regards to some of the major symptoms associated with the climacteric (many of these aspects are discussed in greater detail in other articles in this symposium). Finally we will attempt to place in perspective our current recommendations of the role of estrogen replacement therapy in the postmenopausal patient.

ENDOCRINOLOGIC CHANGES OF THE CLIMACTERIC

Although menopause is the clearest signal of ovarian senescence, ovarian function begins to decline some years before the final menstrual period. Women in their late 30s experience a decreasing frequency of ovulation with accompanying relative infertility and variable menstrual cycles (33). Some years prior to the final cessation of menstruation, the ovary becomes less responsive to gonadotropins (78). Serum estradiol concentrations begin to fall in both the follicular and luteal phases in perimenopausal women (Fig. 1). The decreased levels probably reflect diminished capacity of residual follicles to secrete estradiol since the clearance rate of this hormone does not increase in postmenopausal women (42). The decreasing production of estradiol by the aging ovary leads to a dimunition of the negative feedback upon gonadotropin release, resulting initially in rising serum concentrations of follicle-stimulating hormone (FSH) (Fig. 1) and then later in rising (but more variable) levels of luteinizing hormone (LH) (28). Thus, an early indication of an aging ovary is an increase in circulating FSH and LH and a decrease in serum concentrations of estradiol and progesterone, even before ovulatory cycles cease (66, 67).

In random serum samples from postmenopausal women, FSH levels are more consistently elevated than LH values (28). The quantity of circulating FSH is greater than LH in patients who experience ovarian failure due either to age (28) or to surgical castration (49). In the surgically castrated female the levels of gonadotropin may continue to rise following surgery for a period of up to 2–4 weeks (Fig. 2).

Some perimenopausal women are found to have elevated FSH levels with LH levels in the normal range. Speculation about this discordant regulation of LH

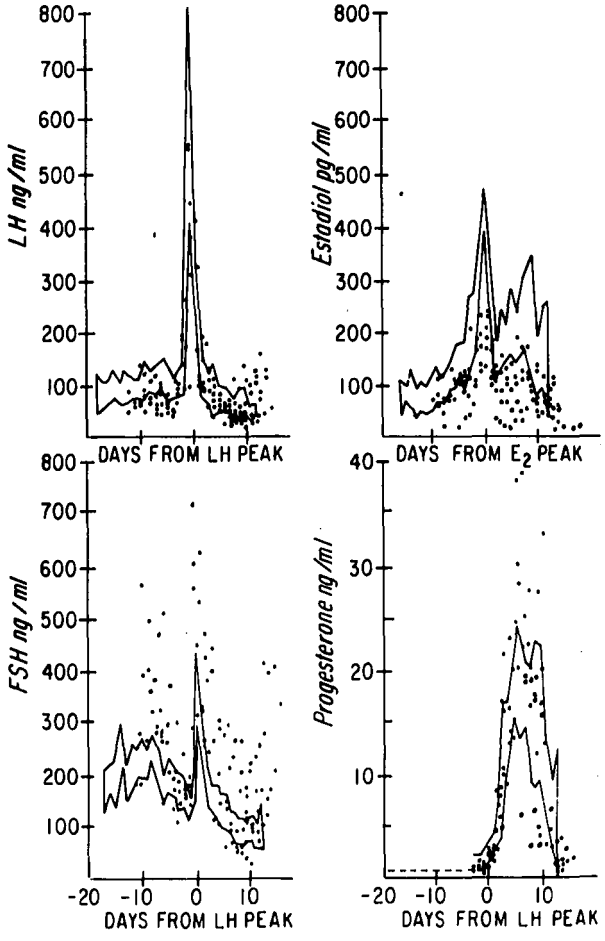


FIG. 1. Serum concentrations of LH, FSH, estradiol, and progesterone in premenopausal women 46–56 years old with regular menses as compared to the mean ± 2 SEM in women 18–20 years old (*enclosed areas*). (Sherman BW, West JH, Korenman SG: The menopausal transition: Analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab 42:629, 1976. Copyright © 1976 by the Endocrine Society)

and FSH suggests the existence of another ovarian regulatory hormone that participates in the modulation of FSH, perhaps a substance analogous to inhibin, which is postulated to exist in men (66, 67). This might also help explain the existence of elevated levels of FSH in some perimenopausal women with relatively normal estradiol levels (30).

As noted above, the increased circulating levels of the gonadotropins are a result of increased pituitary production, since metabolic clearance rates for both gonadotropins are not different for premenopausal and postmenopausal females (8, 36). Periodic pulsatile patterns of LH and FSH are observed in postmenopausal women at 1- to 2-hour intervals and are more prominent than

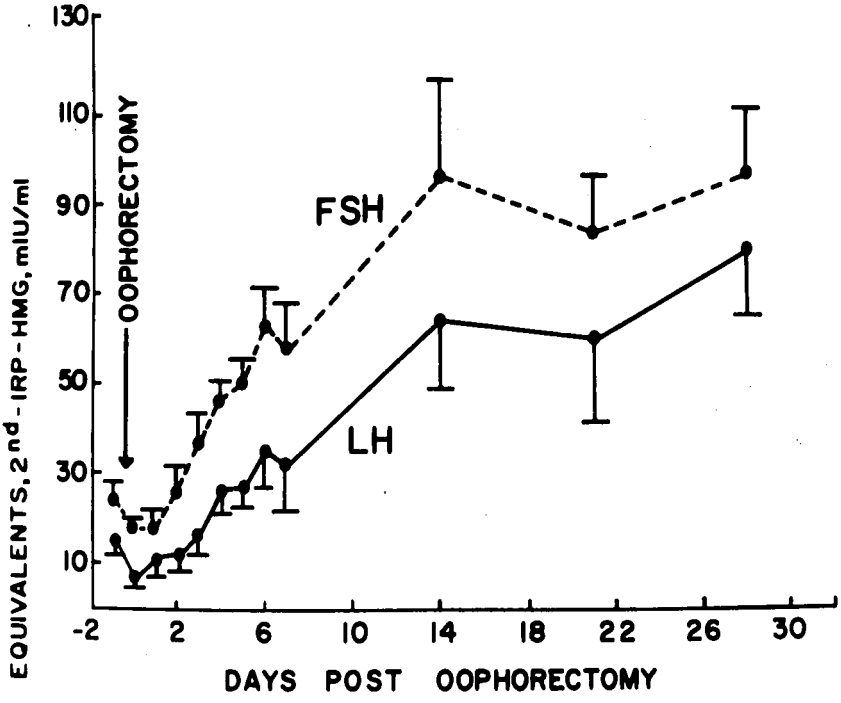


FIG. 2. Mean serum LH and FSH concentrations in six menstruating women prior to and following bilateral oophorectomy and total hysterectomy. The mean serum LH and FSH concentrations for the first 12 hours following oophorectomy depicted by the second set of data points represent 14 different observations in these patients. (Monroe SE, Jaffe RB, Midgley, AR Jr: Regulation of human gonadotropins. XIII. Changes in serum gonadotropins in menstruating women in response to oophorectomy. J Clin Endocrinol Metab 34:420, 1972. Copyright © 1972 by the Endocrine Society)

those seen in women with cyclic menses (79) (Fig. 3). The increased amplitude of pulsatile gonadotropin release may be the result of the greater pituitary responsiveness to gonadotropin-releasing factor (GnRH) in this hypoestrogenic state (69). The increased sensitivity of the pituitary to GnRH has been demonstrated utilizing the synthetic compound to measure pituitary gonadotropin reserve (Fig. 4) and is thought to be due to increased pituitary gonadotropin stores (which is consistent with the finding of increased pituitary gonadotropin content in postmenopausal women) (64).

Thus, with the declining supply of ovarian follicles and the consequent reduced ability of the ovary to produce estrogen in the perimenopausal years, the frequency of ovulatory cycles begins decreasing. There is also altered function of the corpus luteum and reduced progesterone secretion (12). Finally, cycles become anovulatory with changing serum levels of estradiol but essentially no production of progesterone (66).

Estradiol, the most potent biologically active estrogen, is the principal estrogen of the premenopausal female. A marked reduction in the serum

concentration of this hormone, from approximately 120 pg/ml to 18 pg/ml following oophorectomy, strongly suggests that the hormone is primarily secreted by the ovary (30). These data are consistent with values measured in premenopausal and postmenopausal females (78) (Fig. 5). The small amount of estradiol still present in postmenopausal women probably represents extraglandular formation from testosterone and estrone.

Serum levels of estrone are lower than those of estradiol in the premenopausal female. The sources of estrone are complex, consisting of a combination of direct ovarian secretion (68) plus extraglandular formation from both androstenedione (68) (which originates from both the ovary and the adrenal) and estradiol (30). Thus, the fall in serum concentrations of estrone following oophorectomy in premenopausal women (Fig. 6) reflects not only a loss of direct ovarian secretion but also a decrease of its "prehormones."

Some studies that compare ovarian vein concentrations to peripheral levels have suggested that the postmenopausal ovary maintains an ability to produce some estrogen (Fig. 7); however, it must be minimal because there is no significant change following oophorectomy in postmenopausal women (30) (Fig. 8).

The estrone present following oophorectomy is principally derived from peripheral aromatization of androstenedione (20, 68), a process thought to occur principally in adipose tissue. There appears to be a positive correlation between the extent of conversion of androstenedione to estrone and body weight (20) (Fig. 9). The extent of this extragonadal aromatization appears to be influenced also by age, increasing by as much as 100% in certain individuals as they become older (20).

Circulating concentrations of androstenedione decrease in postmenopausal women to levels similar to those found following castration of the premenopausal female (Figs. 5 and 6), suggesting that the postmenopausal ovary does not secrete this hormone. However, data from postmenopausal patients who have undergone oophorectomy demonstrate a small but significant decrease in androstenedione (Fig. 8). Thus menopause is associated with a marked decrease in ovarian androstenedione secretion, but some secretory activity apparently remains, as confirmed also by ovarian vein sampling for this hormone in postmenopausal women (Fig. 7).

In contrast to androstenedione and the estrogens, the postmenopausal ovary continues to secrete substantial quantities of testosterone (31) as evidenced by relatively high concentrations of this hormone in ovarian venous blood compared to the peripheral levels (Fig. 7) and by a significant decrease in serum levels following oophorectomy (Fig. 8). The decrease in testosterone following oophorectomy in postmenopausal women may be due in part to a decline in androstenedione production (which serves as a prehormone for testosterone). Not only does the postmenopausal ovary appear to continue to secrete testosterone, but ovarian testosterone secretion may be even greater in postmenopausal women than in premenopausal women (32), perhaps as a result of stromal stimulation by elevated gonadotropin (31).

In postmenopausal women, the adrenal gland is the major source of androstenedione (which can be peripherally converted to estrone), but the adrenal does not directly secrete appreciable amounts of estrogens, contrary to earlier belief (28, 68). In fact, the normal human adrenal gland secretes very little estrogen at any stage of adult life (25).

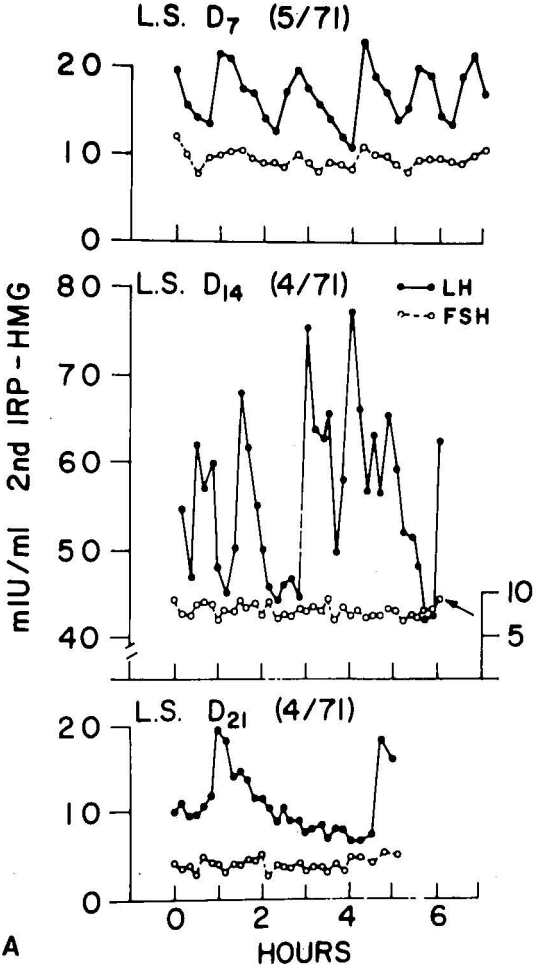


FIG. 3. A. Serum LH and FSH concentrations in samples obtained at 10–15 min intervals during the follicular phase, luteal phase and midcycle surge.

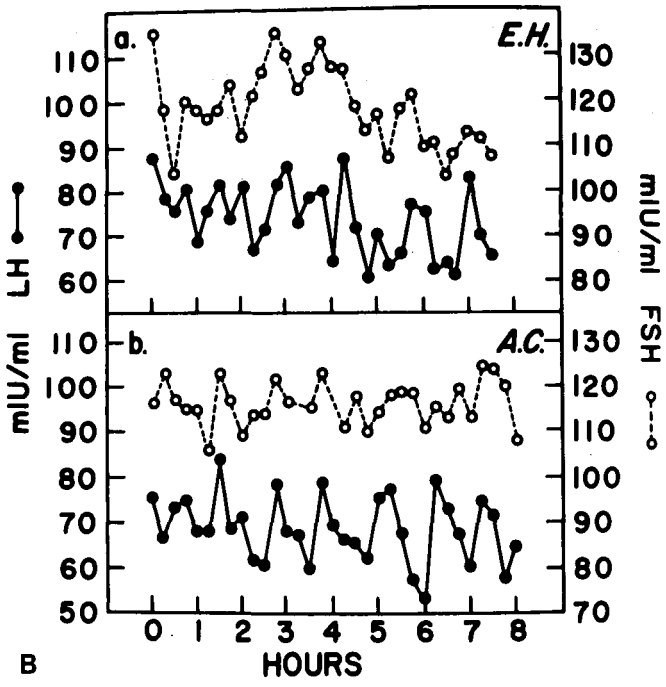


FIG. 3. (cont'd). **B.** Serum LH and FSH concentrations in samples obtained at 10–15 min intervals in two postmenopausal women. Note the frequency and magnitude of pulsations are greater in postmenopausal women. (Yen SSC, Tsai CC, Naftolin F, Vanderburg G, Ajabor L: Pulsatile patterns of gonadotropin release in subjects with and without ovarian function. J Clin Endocrinol Metab 34:671, 1972. Copyright © 1972 by the Endocrine Society).

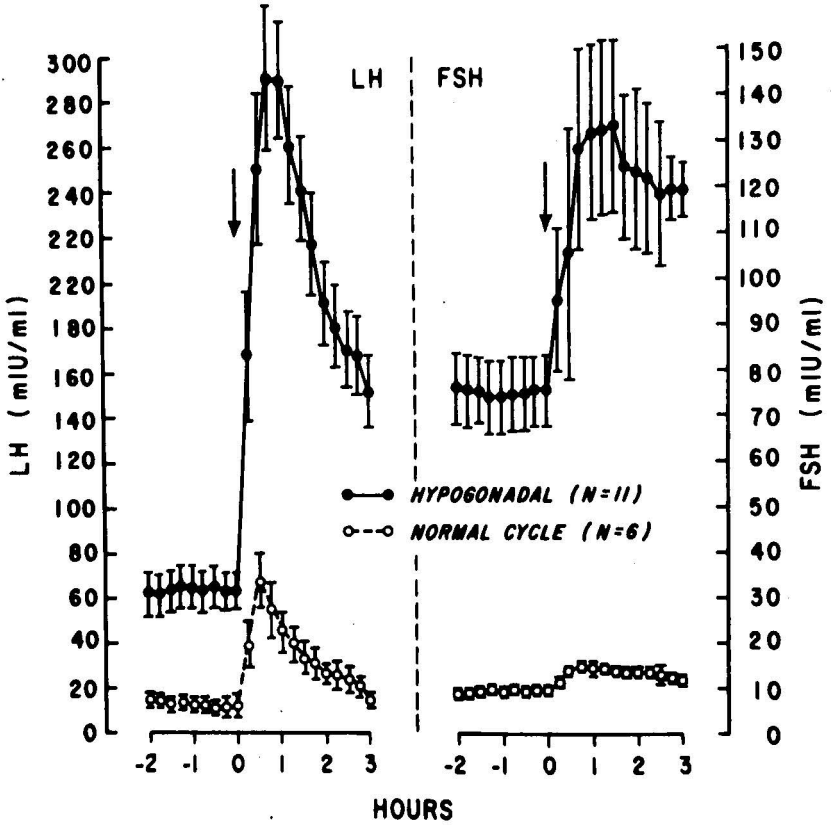


FIG. 4. Following a bolus of LRF (150 μg, IV) the net increase (mean ± SE) above basal levels for serum LH and FSH for 3 hours is compared in hypogonadal women and women during the early follicular phase (LH $p \leq .001$; FSH $p \leq .01$). (Siler TM, Yen SSC: Augmented gonadotropin response to synthetic LRF in hypogonadal state. J Clin Endocrinol Metab 37:491, 1973. Copyright © 1973 by the Endocrine Society).

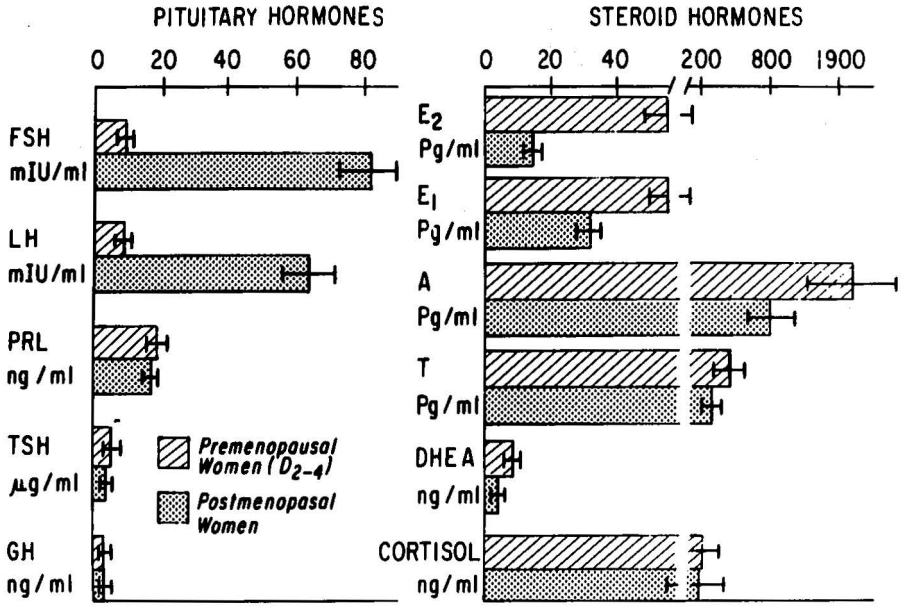


FIG. 5. Circulating levels of pituitary and steroid hormones in premenopausal (cycle days 2–4) and postmenopausal women. (Yen SSC: The biology of menopause. J Reprod Med 18:287, 1977)

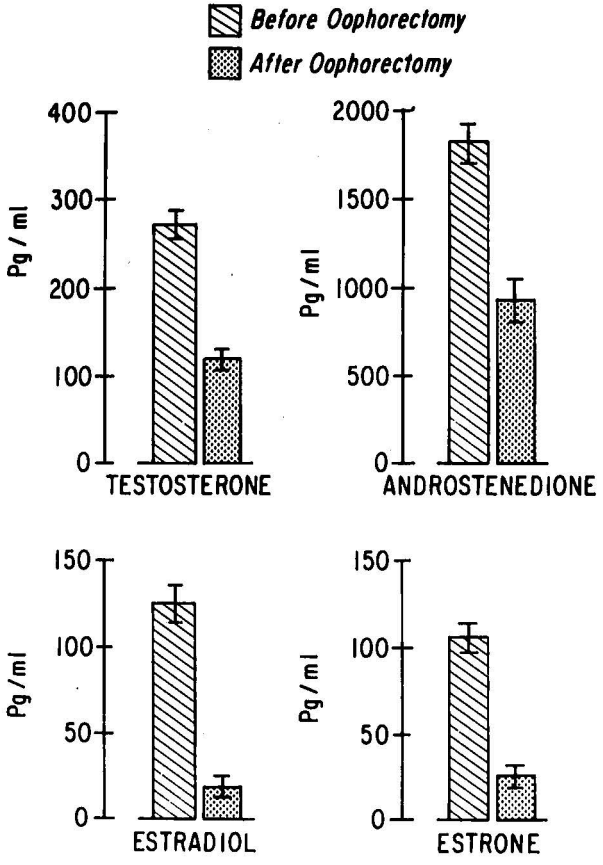


FIG. 6. Serum testosterone, androstenedione, estradiol, and estrone (mean ± SE) in five premenopausal women before and 6–8 weeks after bilateral oophorectomy. (Judd HL: Hormonal dynamics associated with the menopause. Clin Obstet Gynecol 19:775, 1976)

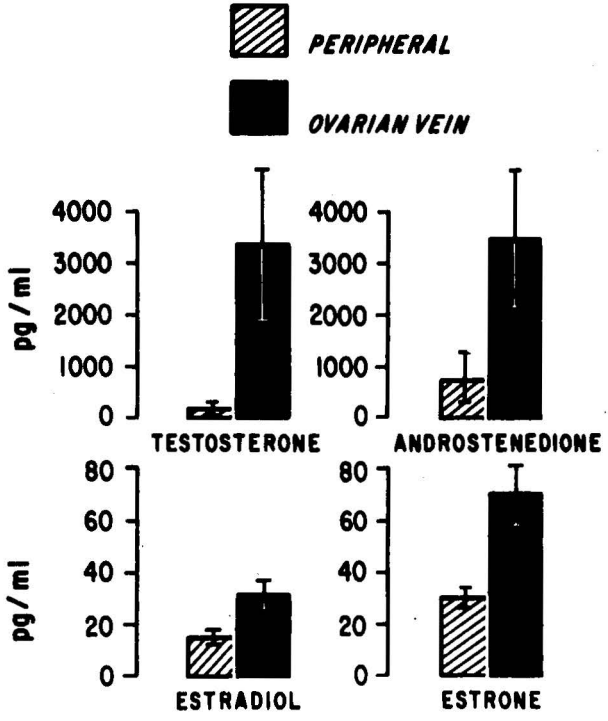


FIG. 7. Peripheral and ovarian vein levels (mean ± SE) of serum testosterone, androstenedione, estradiol, and estrone in 10 postmenopausal women. (Judd HL, Judd GE, Lucas WE, Yen SSC: Endocrine function of the postmenopausal ovary: Concentrations of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 39:1020, 1974. Copyright © 1974 by the Endocrine Society)

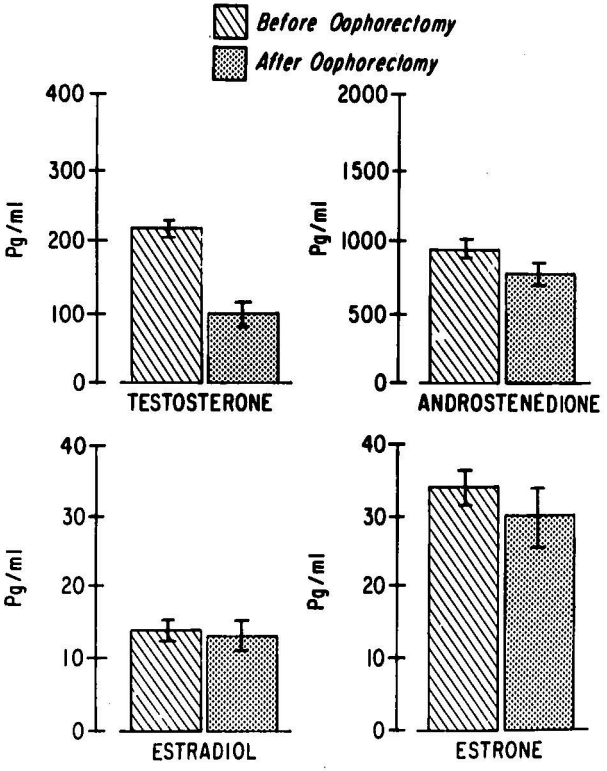


FIG. 8. Serum testosterone, androstenedione, estradiol, and estrone (mean ± SE) in postmenopausal women before and 6–8 weeks after bilateral oophorectomy. (Judd HL: Hormonal dynamics associated with the menopause. Clin Obstet Gynecol 19:775, 1976)

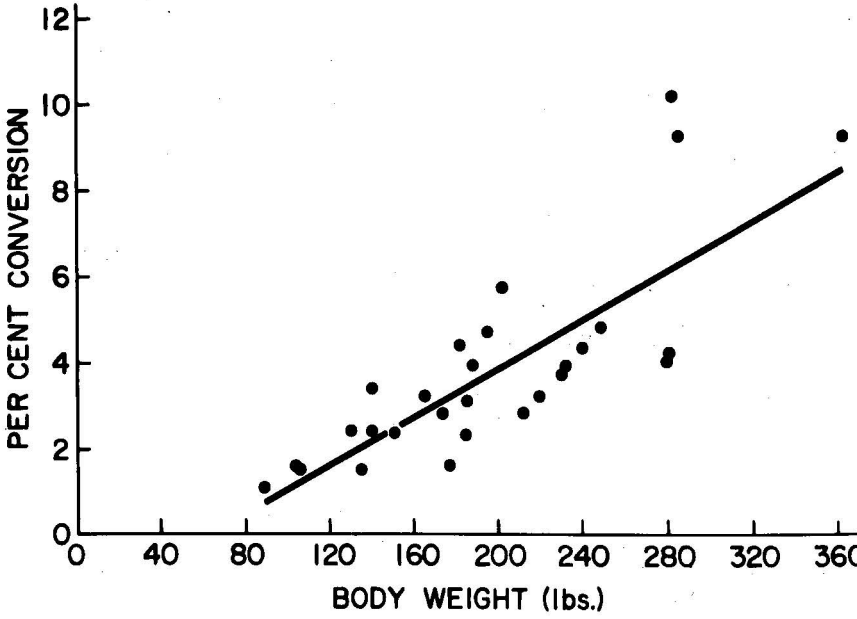


FIG. 9. Correlation of extent of conversion of androstenedione to estrone with body weight in postmenopausal women. Correlation coefficient = 0.74. (Siiteri PK, MacDonald PC: Role of extraglandular estrogen in human endocrinology. In Greep RO, Astwood E (eds): Handbook of Physiology: Endocrinology. Washington DC, American Physiological Society, Vol 2, part 1:615, 1973. Copyright © 1973 by the Endocrine Society)

In summary, the postmenopausal female experiences a decrease in estrogen production, marked elevation of gonadotropins, either no change or a slight decrease in total androgen production. Some of the symptoms of the menopausal syndrome are certainly due to these changes while others may simply relate to the aging process itself.

ADVANTAGES OF ESTROGEN REPLACEMENT (BENEFITS)

In the majority of postmenopausal women the decline in estrogen production is accompanied by signs and symptoms of hormonal deficiency in target tissues. Vasomotor instability and genital atrophy are the most characteristic clinical features. Osteoporosis is another condition now shown to be related at least in part, to the decline in estrogen production. Other symptoms have been less clearly attributed to estrogen deficiency and may simply reflect changes with advancing age.

VASOMOTOR SYMPTOMS

Hot flushes are characterized by a sensation of warmth and heat, and are often accompanied by perspiration. The sensation, which usually starts in the chest and passes upward to the neck, face, and head, can be attributed to withdrawal of estrogen, but social, environmental, and emotional influences also play an important role (78). Hot flushes vary in frequency, intensity, and duration, but they usually subside spontaneously after a few years. The pathophysiology of this vasomotor disturbance is unknown, but the symptom complex suggests a phenomenon of regional vasodilatation with a distribution in accord with cervical sympathetic pathways (78) (see also On the Nature of the Hot Flash, this symposium).

Hot flushes in women who have experienced either spontaneous menopause or surgical castration are associated with elevated gonadotropins, suggesting that hypergonadotropism may be the etiology. Nevertheless, in our experience, only one third of premenopausal women who underwent bilateral oophorectomy developed significant hot flushes, and there was no difference in concentrations of either gonadotropins or estrogens between patients with symptoms and those without (1) (Fig. 10). Also, the estrogen doses generally used to relieve hot flushes are too low to fully suppress gonadotropins (1, 24, 38), and gonadotropins are still elevated in patients in whom hot flushes have spontaneously resolved. Finally, the observation that hot flushes occur after hypophysectomy also suggests that the symptom is not due to increased levels of gonadotropins (50). Interestingly, a patient with elevated gonadotropins who has never had endogenous estrogen production will not have hot flushes unless she receives estrogen replacement therapy and then discontinues the medication (78).

Tataryn et al. correlated the subjective reports of hot flushes with changes in finger skin temperature and plasma gonadotropin concentrations (72) (Fig. 11). They found a close temporal relationship between the perception of a hot flush, a rise in finger skin temperature, and the pulsatile secretion of LH (but not FSH) in postmenopausal women. These investigators felt that hypothalamic factors responsible for the release of GnRH may alter the thermoregulatory centers of

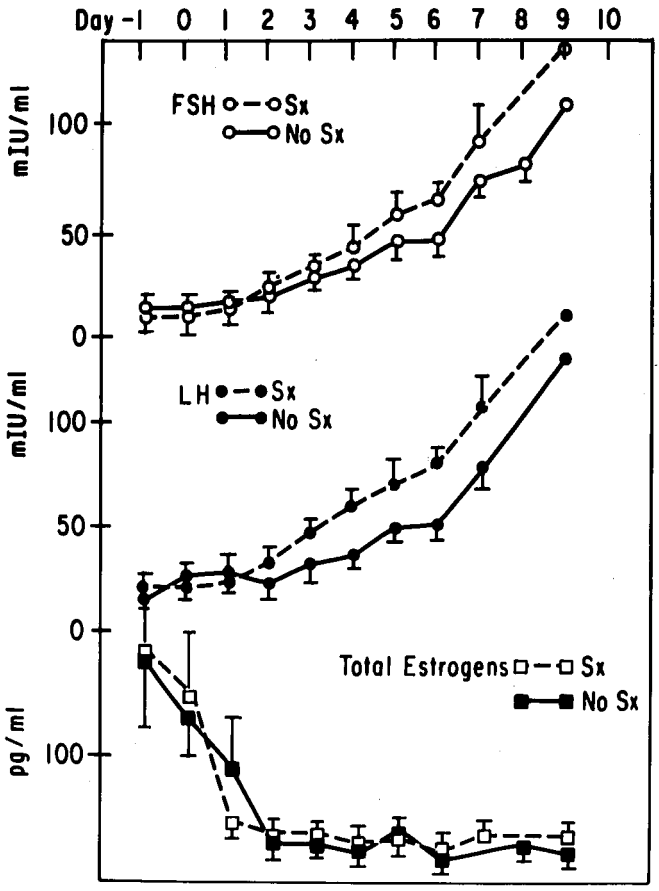


FIG. 10. Serum FSH, LH and total estrogen levels (mean ± SE) in 16 premenopausal women undergoing bilateral oophorectomy on day 0. (Aksel S, Schomberg DW, Tyrey L, Hammond CB: Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause. Am J Obstet Gynecol 126:165, 1976)

the hypothalamus and thereby initiate the hot flush, since GnRH neurons are in close proximity to thermoregulatory center in the preoptic anterior hypothalamus.

Although the precise etiology of the hot flush is not known, estrogen replacement is the most specific and effective therapy. Therapy is begun at a dose sufficient to relieve symptoms; it usually can be decreased in stepwise fashion over months and ultimately discontinued. Although other medications, such as depo-medroxyprogesterone acetate, may be appropriate when estrogen is contraindicated, none approaches the effectiveness of estrogen (60).

ATROPHIC GENITOURINARY CHANGES

Atrophy of the vagina and vulva eventually follows declining estrogen production. The vulvar epithelium becomes progressively thinner and is more

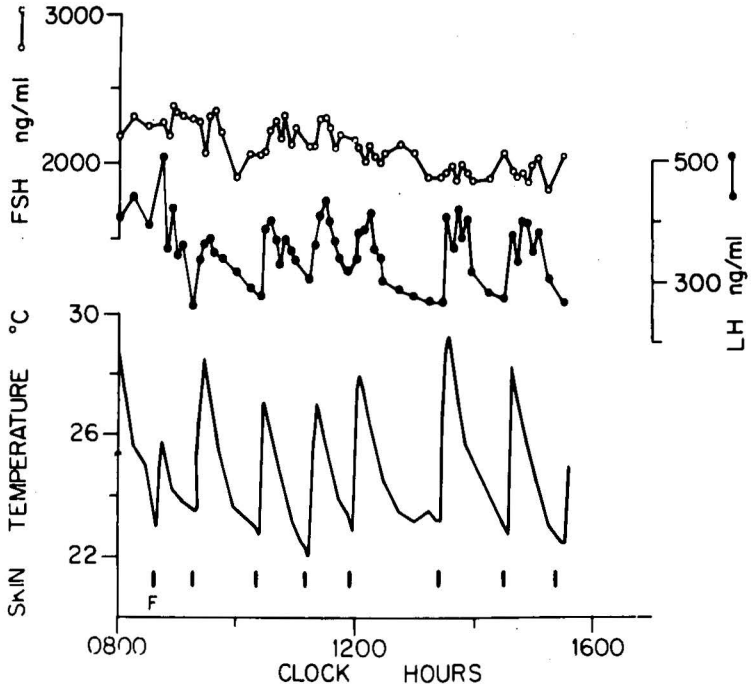


FIG. 11. Changes in cutaneous finger temperature and serum LH and FSH levels. Note close temporal relationship between each subjective hot flash (indicated by *vertical bars*), cutaneous temperature elevation, and pulsatile LH release. (Tataryn IV, Meldrum DR, Lu KH, Frumar AM, Judd HL: LH, FSH and skin temperature during the menopausal hot flash. J Clin Endocrinol Metab 49:152, 1979. Copyright © 1979 by the Endocrine Society)

easily traumatized, but in most instances it remains asymptomatic. As age advances, these changes may become pathologic and contracture of the introitus may lead to dyspareunia. Although vulvar dystrophies (kraurosis vulvae, leukoplakia, lichen sclerosis et atrophicus) and pruritis are more common in postmenopausal women, there are no data to implicate estrogen deficiency as the etiology (52).

Another eventual result of declining estrogen production is vaginal shortening, narrowing, and loss of elasticity. The thin, glycogen-deficient, relatively alkaline vaginal epithelium of the postmenopausal woman is more prone to ulceration and infection (52). These changes, which may cause symptoms of dyspareunia and vaginal irritation, are usually referred to as atrophic vaginitis. However, it should not be forgotten that vaginitis in the postmenopausal female may be due instead to pathogens such as *Trichimonas vaginalis, candida albicans* and *Hemophilis vaginalis.*

In addition to the genital tract, the urethral and bladder trigone are also responsive to estrogen. This observation is not surprising because these tissues possess a similar embryologic origin. As estrogen production declines, the urethra may become less distensible and more easily traumatized. This urethral

change may be associated with recurrent urethritis (the "urethral syndrome" or abacterial recurrent urethritis) (6). Atrophic changes of the lower urinary tract and alterations of bacterial flora of the vagina predispose to an increased incidence of urinary tract infections in postmenopausal women. In addition, the incidence may be further increased by larger residual urine volumes, which result from less efficient bladder emptying (5) and neurogenic bladder changes (37).

There is marked variability in the onset and severity of atrophy of the urogenital tissues. This is in part due to variations in the rate of decline of estrogen production, which may be acutely or chronically muted by factors that increase either prehormone production or efficiency of conversion of prehormone to estrone (33). Some women may become symptomatic in months, others take years to develop symptoms or urogenital atrophy, and some never develop such symptoms.

Estrogens have a proliferative effect on the urethral epithelium and on elastic and connective tissues; hence they are quite effective in management of patients with the "urethral syndrome" (6, 53). Estrogen therapy will also induce proliferation of the vaginal epithelium, resulting in relief of symptoms from atrophic vaginitis and frictional dyspareunia, and can be administered either systemically or directly to the vagina as a cream. Thus, estrogen therapy is effective in alleviating the majority of the symptoms of urogenital atrophy.

OSTEOPOROSIS

Osteoporosis, a reduction in bone mass and density, is more common in postmenopausal women than in comparably aged men. Albright et al. suggested an association of osteoporosis with menopause and postulated that this disorder was due to deficient bone formation caused by failure of osteoblastic activity (2). However, osteoporosis appears to result primarily from increased bone resorption, which may be caused partially by prolonged negative calcium balance, and not from decreased bone formation (23, 28, 78).

In both sexes, bone mass reaches its peak at approximately age 35 (33). At any age mean, bone mass is greater in men than in women (Fig. 12) (48) and greater in blacks than in whites (15). Within these groups, however, certain patients will develop osteoporosis and others will not, and it is notoriously difficult to predict which patients will develop the problem. Once adulthood is reached, bone mass plateaus for several years, then begins to decline. As shown in Figure 12, the rate of loss is much greater for women than men (15, 23, 33, 47). In women, bone demineralization is correlated more closely with loss of ovarian function than with age, and bone loss begins correspondingly earlier in surgically castrated women (15, 23, 28, 48). Meema et al. found that women over 50 who were still menstruating did not demonstrate any decline in bone mineral mass, while postmenopausal women, regardless of age, showed a significant loss of bone mass in proportion to the number of years after menopause (47) (Fig. 13).

Osteoporosis per se does not produce symptoms, but the structural changes and fragility of bones that result predispose to bone fracture, particularly of the vertebral bodies (15). Approximately 25% of all white women over age 60 have spinal compression fractures due to osteoporosis (23). One of the most severe sequelae of osteoporosis is hip fracture; approximately 15% of patients die within 3 months of such injury and the survivors often experience deterioration

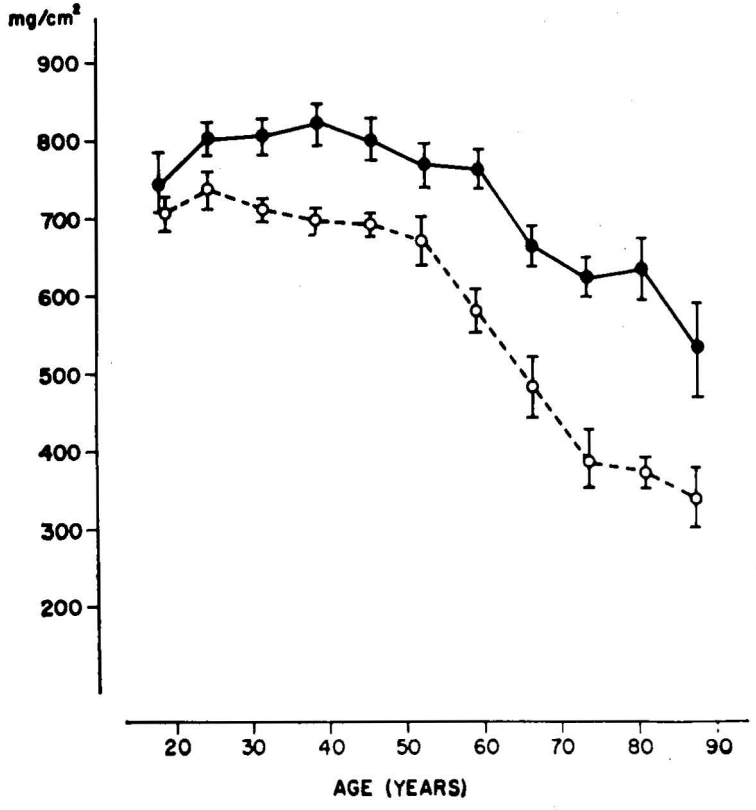


FIG. 12. Bone mineral mass (mean ± SE) of the radius, determined by photosensitivity, in 305 normal men (•) and 308 normal women (○). (Meema S, Meema HE: Menopausal bone loss and estrogen replacement. Israel J Med Sci 12:601, 1976)

in quality of life (3). The temporal relationship between menopause and the development of osteoporosis (Fig. 13) suggests that estrogen deficiency may play a role in the process of loss of bone mass. Estrogen-deficient postmenopausal women exhibit a slight elevation in both plasma and urinary calcium and an associated increase in urinary hydroxyproline excretion, which is generally thought to reflect bone resorption.

The accelerated loss of bone mineral mass in estrogen-deficient women can be prevented by administering estrogens orally (28). In fact, estrogen therapy may even promote a slight increase in bone mineral mass (49) (Fig. 14). Lindsay et al. prospectively studied metacarpal mineral content in two groups of women surgically castrated before the menopause. One group took mestranol (20 μg daily) for five years after castration, while the other women received a placebo. As shown in Figure 15, a significant difference was seen as early as 1 year after castration.

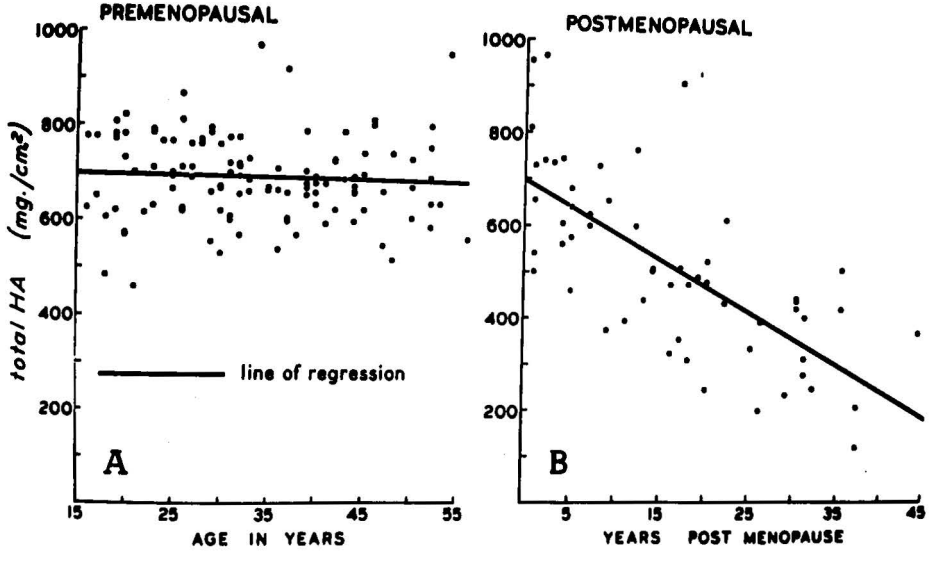
Thus estrogen replacement may be instrumental in the prevention of osteoporosis, but the exact mechanism of this benefit is not clearly understood. Many investigators believe that estrogens inhibit parathyroid hormone activity

and thus inhibit bone resorption, resulting in a decreased rate of bone loss (15, 23, 28, 33, 78). It is also possible that estrogens stimulate calcitonin activity, but the role of estrogens in modulating calcitonin function has not been fully elucidated. Nevertheless, the dosage of estrogen needed to maintain bone mineral mass appears to be as little as 20 μg of mestranol per day, or the equivalent, and may even be less.

Estrogen therapy in patients with established osteoporosis may prevent further bone loss but there is no evidence that estrogen reverses to a detectable extent the bone loss that has already occurred (23). Therefore to be of the most benefit, replacement therapy should be initiated before serious loss of bone density occurs. The problem surrounding the prophylactic use of estrogen therapy for this indication is our relative inability to predict which women will develop osteoporosis. Nevertheless, instead of treating all postmenopausal women prophylactically with estrogen it is probably advisable to limit therapy to those patients who are frail and fair-skinned or to those whose older female relatives suffered debilitating osteoporosis and fractures (23). Cessation of estrogen therapy, even after long periods, results in progressive loss of bone mineral content (40) (Fig. 16). Thus, it would appear that estrogen replacement for prophylaxis against osteoporosis should be administered indefinitely. Equally as difficult as predicting who will develop osteoporosis is the problem of identifying and following osteoporotic changes in postmenopausal women. Meema and Meema have suggested following bone mass radiographically (48), but it is not clear which method they considered best.

Although estrogen replacement therapy appears to diminish the rate of bone matrix loss it is unclear whether the hormone significantly decreases the

FIG. 13. Bone mineral mass (as measured by total hydroxyapatite content) in premenopausal women in relation to age (A) and in normal postmenopausal women in relation to number of years following menopause (B). (Meema HE, Bunker ML, Meema S: Loss of compact bone due to menopause. Obstet Gynecol 26:333, 1965)



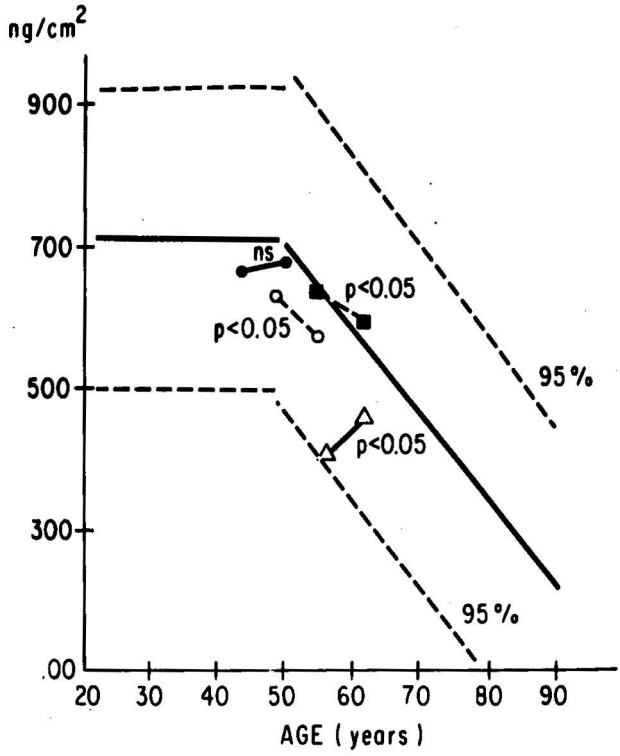


FIG. 14. Changes in bone mineral mass of the radius in two groups of nontreated and two groups of estrogen-treated postmenopausal women in relation to the mean (*solid line*) and 95% confidence limits (*broken line*) of normal women. ■-----■ natural menopause (untreated), o-----o surgical menopause (untreated); Δ----Δ natural menopause (estrogen treated); •-----• castrates (estrogen treated). (Meema S, HE: Menopausal bone loss and estrogen replacement. Israel J Med Sci 12:601, 1976)

incidence of fractures in estrogen-deficient women. Nevertheless, there is suggestive evidence of a decrease in the incidence of both osteoporosis and fractures in younger women who received estrogen replacement therapy after loss of endogenous estrogen production (21). It is important to realize that other factors such as exercise, and dietary intake of calcium, fluoride, and vitamin D play an important role in this disease. Furthermore, there is some evidence that progestogens may inhibit bone loss in postmenopausal women (41) (see also Age, Estrogen, and Bone Density, this symposium).

ATHEROSCLEROSIS

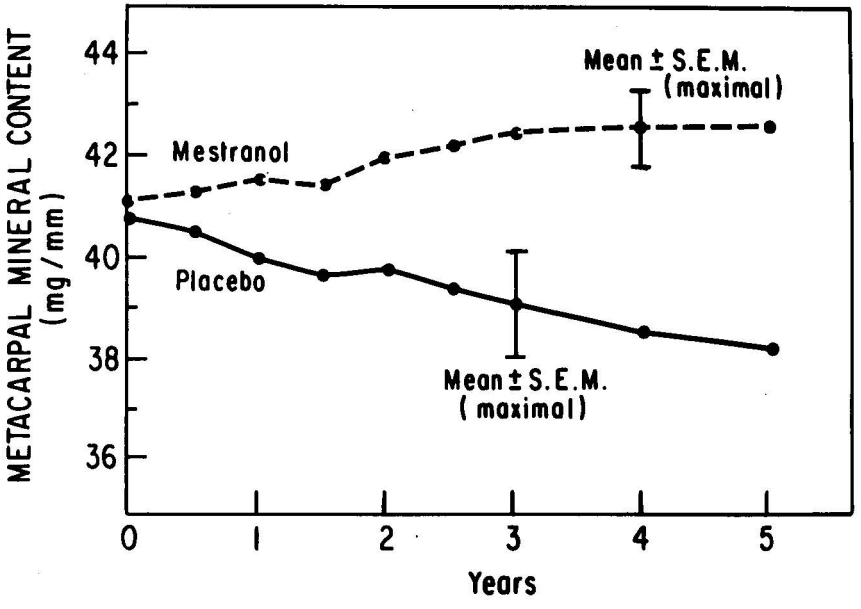
Due to conflicting information in the literature, the exact role of estrogens in the pathogenesis of atherosclerosis and myocardial infarction remains unclear. A relationship between the increased incidence of atherosclerosis (and thus myocardial infarction [55]) and decreased estrogen production suggests that estrogens protect against development of this disease (Fig. 17). Elevated serum levels of low-density lipoprotein and cholesterol (thought to be associated with an increased risk of atherosclerotic disease [63, 77]) can be reduced by estrogen

administration (63). Tikkanen et al. reported an average 22% reduction in low-density lipoprotein cholesterol concentration and a 30% increase in the high-density lipoprotein cholesterol concentration with administration of estradiol valerate.

The theory that estrogen might protect against the development or progression of cardiovascular disease led to its use in male survivors of myocardial infarction as well as in menopausal women. Unfortunately estrogens were not found to be protective in the male survivors of myocardial infarction but instead were associated with an increased risk of recurrence (9, 10). Although some have found that estrogen treatment often leads to a pattern of serum lipoproteins characteristic of groups at low risk to develop atherosclerosis, there is no strong evidence that postmenopausal administration of estrogen serves to retard the development of this vascular lesion. The data continue to be controversial. Various investigators have reported detrimental effects (17), beneficial effects (21), or no effect (51, 59) of estrogen replacement therapy on the development of coronary artery disease in postmenopausal women.

In contrast to the postmenopausal woman, it appears that estrogen replacement should be provided for young women who undergo oophorectomy or who experience premature ovarian failure (63). Autopsy data from women who underwent castration up to 15 years before death were compared with data from noncastrated controls matched for age and race (56). Excessive coronary atherosclerosis was seen when castration was performed before age 40 and the

FIG. 15. Mean metacarpal mineral content of two groups of patients following bilateral oophorectomy at time zero. (Lindsay R, Hart DM, Aitken JM, MacDonald EB, Anderson JB, Clarke AC: Long-term prevention of postmenopausal osteoporosis by oestrogen: Evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet 1:1038, 1976)



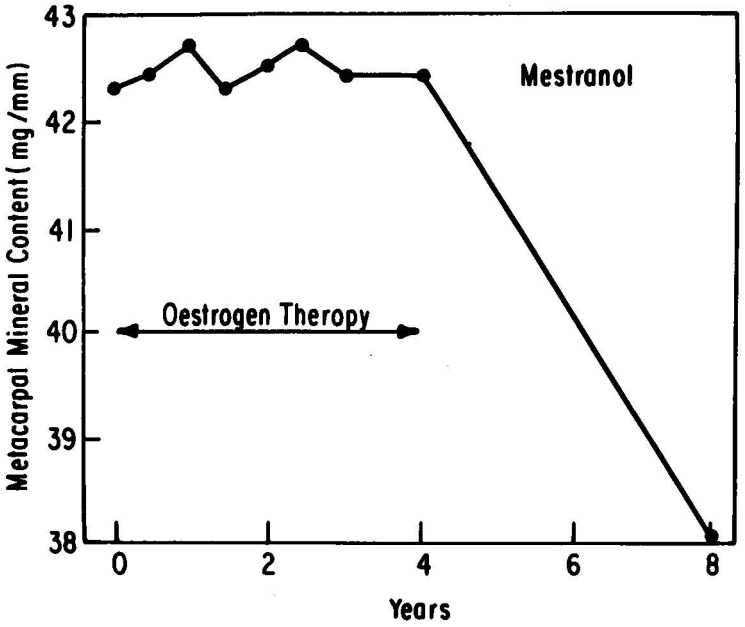
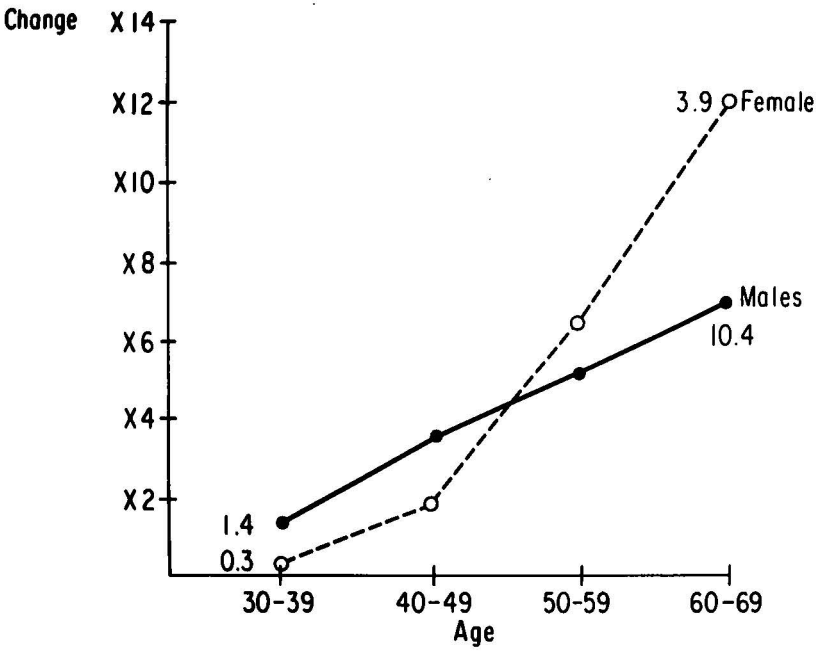


FIG. 16. Effects of withdrawal of estrogen therapy on bone mineral content after 4 years of therapy. (Lindsay R, Hart DM, Maclean A, et al: Bone response to termination of oestrogen treatment. Lancet 1:1325, 1978)

FIG. 17. Change in incidence rates of acute myocardial infarction per 1000 by age and sex. (Oliver MF: The menopause and coronary heart disease. In Campbell (ed) The Management of the Menopause and Postmenopausal Years. University Park Press, Baltimore, 1976 p 177)



individual survived 14 years or longer beyond operation without estrogen replacement. These data, supported by clinical observations (21), suggest that estrogen replacement may be of significant value to the young woman with premature loss of estrogen production.

DYSFUNCTIONAL UTERINE BLEEDING

As menstrual cycles preceding menopause become either anovulatory or associated with insufficient corpus luteum function (and insufficient progesterone secretion), the pattern of bleeding often becomes irregular. This irregular bleeding is usually due to either estrogen breakthrough or estrogen withdrawal, and it may be prolonged and profuse, since the normal mechanisms for cessation of menstrual bleeding are absent (specifically, the influence of progesterone). Because of the increasing incidence of endometrial neoplasia with age, evaluation of the patient should include an adequate histologic evaluation of the endometrium.

Appropriate hormonal management after the exclusion of neoplasia includes the use of progestogens to produce stabilization and regression of the endometrium and to induce an orderly bleeding episode when withdrawal occurs. Typical drug regimens include medroxyprogesterone acetate (Provera), 10–20 mg daily, or norethindrone acetate (Norlutate), 10 mg daily, for 5–20 days each month. Usually, supplemental estrogen is not needed at this time. A lack of response of abnormal bleeding to appropriate hormonal therapy suggests an organic (nonfunctional) cause of the uterine bleeding and further investigation is warranted.

NONSPECIFIC SYMPTOMATOLOGY

Amenorrhea, the hot flush, and atrophic vaginitis should be regarded as logical manifestations of menopause, whereas other symptoms are often due to more complex factors associated with aging, such as the challenge of adapting to changing roles and functions. Other symptoms that have been commonly associated with menopause include headaches, irritability, mood changes, and nervousness. These usually do not respond to estrogen replacement and should be treated, if necessary, with specific therapy. Estrogen therapy should be reserved to treat symptoms of estrogen deficiency.

DISADVANTAGES OF ESTROGEN REPLACEMENTS (RISKS)

ENDOMETRIAL NEOPLASIA

An association of elevated endogenous estrogens and the increased likelihood of endometrial carcinoma has been suspected for many years (54). A high incidence of abnormal endometrial findings has been observed in patients with certain constitutional stigmas. Adenomatous hyperplasia and endometrial carcinoma appear at an increased rate in proportion to aging and obesity; those lesions also develop inappropriately early in premenopausal women with polycystic ovarian disease or functioning ovarian tumors (33) but are rarely seen in individuals with vasomotor symptoms or atrophic vaginitis.

Because of the clinical correlation between estrogens and endometrial cancer, particular attention has been directed toward identification of a causal relationship between estrogen therapy and endometrial cancer. In several studies of postmenopausal women, the incidence rates of endometrial carcinoma in estrogen users were found to be 3.8 to 12.5 times the rate in matched controls not receiving the compounds (18, 22, 45, 46, 70, 80) (Table 1). In many of these studies, the risk ratio was related to the dose of estrogen and duration of therapy. Other investigators have not found evidence to suggest a causal relationship (13, 19) or have drawn attention to flaws in the design of prior studies that tend to negate their conclusions (16, 27).

Although Hammond et al. reported an increased risk of developing endometrial carcinoma associated with estrogen replacement therapy, none of 207 women with uteri in situ who also regularly received a progestin (72 women) developed endometrial cancer (22). Progesterone has been shown to inhibit the replenishment of estradiol receptors (26), thereby reducing both estrogen uptake and the unopposed stimulation of target cells by estrogen. This finding plus the clinical observation of regression of endometrial hyperplasia following progestin therapy (61) may explain the apparent protective effect of progestin administered in conjunction with estrogen replacement therapy. The use of a progestin along with estrogen therapy does not appear to reduce the benefits of the estrogen treatment (21).

In summary, postmenopausal women who receive estrogen replacement therapy do appear to at increased risk for developing endometrial neoplasia, but the risk may be significantly reduced by adding a progestin and monitoring the endometrium carefully.

THROMBOEMBOLISM

There is strong evidence that in certain settings high-dose estrogen replacement therapy can increase the risk of thromboembolic disease (77), cerebrovascular accidents, and coronary artery disease. The effects are dose related and increase with age (33). It has been shown that estrogen administered for postpartum lactation increases the risk of thromboembolism and that the risk is greater in older parturients (11). The risk is further increased if the woman smokes. In fact, some investigators have considered smoking a contraindication for the use of oral contraceptive agents (58). Although Gitel and Wessler reported an increase in coagulability in postmenopausal females on estrogen replacement therapy (14), there is no conclusive evidence that the use of low-

TABLE 1. ENDOMETRIAL CARCINOMA AND EXPOSURE TO EXOGENOUS ESTROGEN

Authors (ref)	Date	Retrospective incidence rate (relative risk)
Smith et al. (70)	1975	7.5
Ziel and Finkle (80)	1975	7.6
Mack et al (45)	1976	8.0
McDonald et al. (46)	1977	7.9
Gray et al. (18)	1977	12.7
Hammond et al. (22)	1979	3.8

dose estrogen replacement therapy significantly increases the risk of thromboembolism. Two studies reported no increased risk of venous thromboembolism in postmenopausal women receiving estrogen replacement (4, 57). The absence of association between noncontraceptive estrogens and venous thromboembolism is thought to be due to the low dose of estrogen rather than to differences in thrombogenic potential of different estrogens (57).

RECOMMENDATIONS

Major contraindications to the use of any estrogen therapy include estrogen-dependent neoplasia (of breast or endometrium), history of thrombophlebitis or thromboembolus, and active or severe liver disease. Prior to the initiation of estrogen therapy, the physician should take a thorough history and perform a thorough physical examination. Estrogen therapy should be considered only if the patient is clearly estrogen deficient. A progesterone challenge test, a vaginal smear for maturation index, and an examination of cervical mucus for ferning may be helpful in this portion of the assessment (76). A full discussion with the patient is mandatory so that she is aware of the benefits and risks of estrogen therapy and understands the specific goals of therapy.

If a decision is made to initiate estrogen replacement therapy then the treatment should be begun with the lowest available dose (i.e., 0.3 mg conjugated estrogens or 0.01 mg ethinyl estradiol); if necessary, the dosage may be increased in a stepwise fashion until the desired effect is achieved. There appears to be no difference in the therapeutic efficacy between natural and synthetic estrogens (35). Estrogens are administered cyclically (i.e., 21–25 days out of each calendar month) and a progestin (i.e., medroxyprogesterone acetate [Provera], 10 mg) should be added during the last 7–10 days of estrogen therapy if the patient has a uterus (12, 22, 33, 51).

Estrogen replacement therapy is recommended for all women who prematurely lose (or do not have) their ovarian source of estrogen before age 40 (i.e., patients with gonadal dysgenesis or premature ovarian failure and those who underwent surgical menopause), unless contraindicated, to prevent premature development of osteoporosis and atherosclerosis.

Although vasomotor symptoms may decrease spontaneously over a period of a few years, estrogen replacement therapy may be indicated initially for symptomatic treatment. Usually the dose of medication can be decreased periodically and eventually discontinued, so that replacement therapy for this indication is typically short term.

Symptoms of urogenital atrophy, such as atrophic vaginitis and the "urethral syndrome" respond well to low-dose estrogen replacement. In general the relief of symptoms of urogenital atrophy usually requires less estrogen than is required to relieve vasomotor symptoms. For these indications, topical creams containing estrogen may be more convenient and are often needed only 2 or 3 times a week. Estrogens in these vaginal creams (estrone and estradiol) are systemically absorbed, however, yielding physiologic premenopausal levels of estrogens that can suppress serum gonadotropins as much as 30% (62, 65) (Fig. 18). Moreover, estrogens absorbed vaginally can produce both endometrial stimulation and bleeding (71). Thus, estrogen administration by the vaginal route is subject to the same contraindications and safeguards as the oral route,

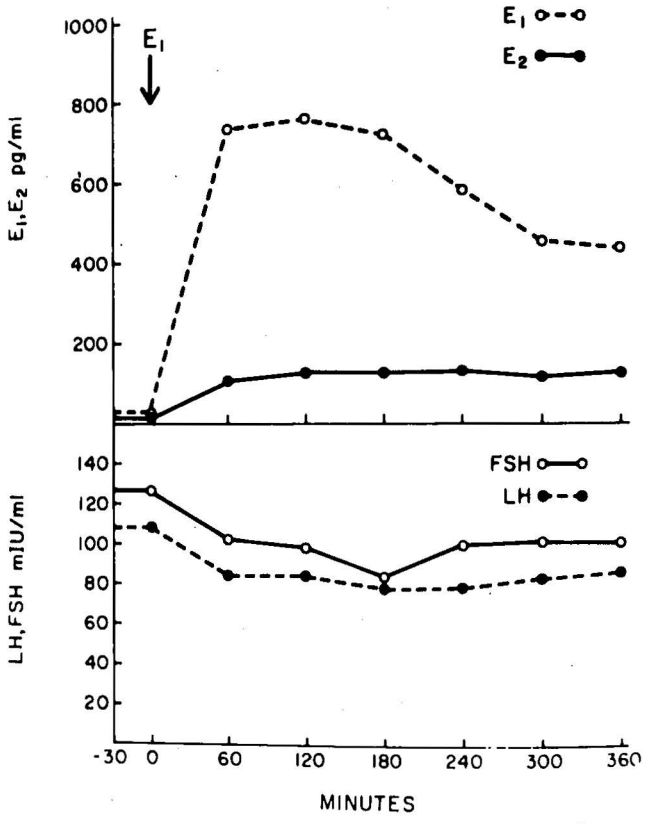


FIG. 18. A. Plasma FSH, LH, estradiol and estrone concentrations before and after vaginal administration of 0.05 mg estrone.

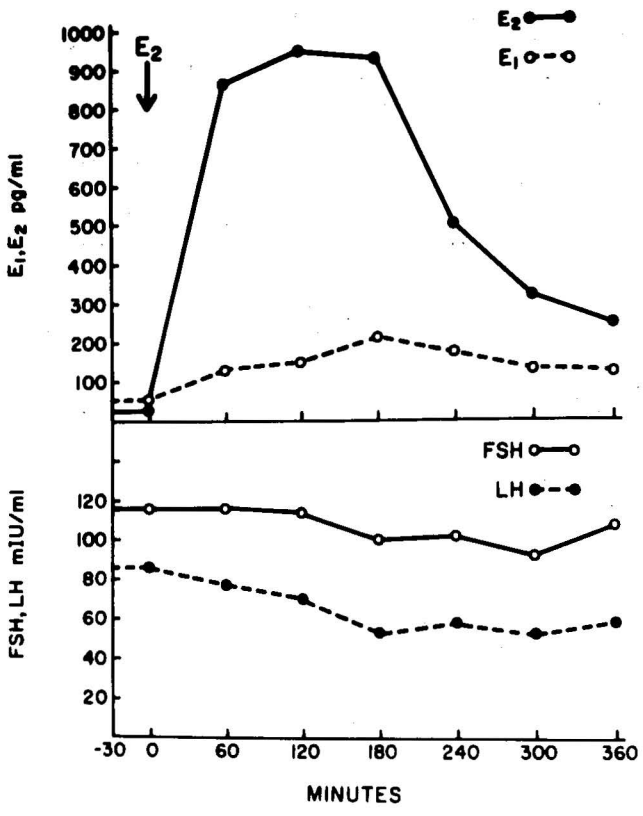


FIG. 18. (cont'd). **B.** Plasma FSH, LH, estradiol, and estrone concentrations before and after 0.5 mg of micronized estradiol. (Schiff I, Tulchinsky D, Ryan KJ: Vaginal absorption of estrone and 17 β-estradiol. Fertil Steril 28:1063, 1977. Reproduced with permission of the publisher, The American Fertility Society)

and consideration should be given to cyclic administration of progestogens in such patients if they have a uterus.

If vaginal bleeding occurs in a postmenopausal woman, endometrial sampling should be performed whether or not she is taking estrogen, but especially if bleeding occurs during the days she is taking the hormone. If sampling of endometrium is by biopsy and any abnormality is discovered, a complete curettage is also needed. If bleeding is due to cyclic estrogen withdrawal, then a reduction in the dose of estrogen used for replacement may solve the problem. Sufficient data do not exist to determine whether or not periodic endometrial sampling on a routine basis in a nonbleeding patient is necessary.

At present, no therapeutic regimen will guarantee freedom from estrogen-induced bleeding. Because smaller doses of estrogen are less likely to produce endometrial stimulation and result in bleeding, the smallest dose should be used initially and it should be increased only if symptoms are not adequately relieved.

The use of injectable or implantable estrogen for the relief of estrogen deficiency symptoms is very effective. However, the length of action is unpredictable, and if a problem develops, the therapy cannot be terminated because the medication cannot be retrieved. Thus, we feel it is advisable to use the oral or vaginal route for replacement therapy.

Data are not available either to support or deny the advantages of combined therapy with androgen–estrogen medications during menopause. Such medications are said to exert an anabolic effect on bone tissues, to restore or improve libido, and, possibly, to permit a reduction in the dose of estrogen (resulting in a diminished tendency for endometrial stimulation). However, androgens may produce an undesired effect on lipoprotein-cholesterol ratios and thus may increase the tendency to develop atherosclerosis. Some or all of these observations may be true, but controlled studies are not available to support utilization of combined therapy (34).

Patients who complain of vasomotor symptoms and have contraindications for estrogen replacement therapy may benefit from depo-medroxyprogesterone acetate (Depo-Provera) (7). As stated earlier, the use of progestins may also be of some benefit in osteoporosis (41), but at this time, data are insufficient to allow a definite conclusion.

SUMMARY AND CONCLUSIONS

Although the administration of estrogen to a postmenopausal woman is not without risk, its use should not be withheld from an appropriately selected, symptomatic patient. Informed consent is mandatory to ensure that the woman is aware of the possible increased risk of endometrial neoplasia and recognizes the fact that symptoms of estrogen deficiency are not life threatening. She must understand that any vaginal bleeding must be reported to the physician to insure prompt investigation, when indicated. In general, it is our opinion that with an appropriate indication in the well-informed patient who does not have a contraindication to its use, the benefits of estrogen replacement therapy outweigh the attendant risks. Estrogen should be administered at the lowest effective dose to alleviate the symptomatology and in a cyclic fashion; a progestogen should be added at the end of each cycle of estrogen therapy if the uterus is present. Vaginal bleeding should be promptly investigated.

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